=> "treatment (l) HBV"
L1 0 "TREATMENT (L) HBV"

=> "treat4 (l) "hepatitis B virus"
L2 4205 4 (L) "HEPATITIS B VIRUS"

=> calcium (l) L2
L3 9 CALCIUM (L) L2

=> cyclosporin and L2
L4 9 CYCLOSPORIN AND L2

=> BAPTA and L2
L5 0 BAPTA AND L2

=> D L3 IBIB ABS 1-9
=> HBV and calcium (w) inhibitor
L6 1 HBV AND CALCIUM (W) INHIBITOR

=> HBV and EGTA
L7 2 HBV AND EGTA

=> D L7 IBIB ABS 1-2

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:526751 CAPLUS

DOCUMENT NUMBER: 139:173263

TITLE: Activation and inhibition of cellular calcium and tyrosine kinase signaling pathways identify targets of the HBx protein involved in hepatitis B virus replication

AUTHOR(S): Bouchard, Michael J.; Puro, Robyn J.; Wang, Lihua; Schneider, Robert J.

CORPORATE SOURCE: Department of Microbiology, New York University School of Medicine, New York, NY, 10016, USA

SOURCE: Journal of Virology (2003), 77(14), 7713-7719
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human hepatitis B virus (**HBV**) HBx protein is a multifunctional protein that activates cellular signaling pathways and is thought to be essential for viral infection. Woodchuck **HBV** mutants that lack HBx are unable to replicate in vivo or are severely impaired. **HBV** replication in HepG2 cells, a human hepatoblastoma cell line, is stimulated 5- to 10-fold by HBx protein. We have utilized the HepG2, HBx-dependent **HBV** replication system to study the effects of activators and inhibitors of cytosolic calcium and tyrosine kinase signaling pathways on viral replication. By transfecting either a wild-type **HBV** genome or an **HBV** genome that does not express HBx and then treating transfected cells with activators or inhibitors of signaling pathways, we identified compds. that either impair wild-type **HBV** replication or rescue HBx-deficient **HBV** replication. Geldanamycin or herbimycin A, tyrosine kinase inhibitors, blocked **HBV** replication. Derivs. of cyclosporine, i.e., cyclosporine A, cyclosporine H, and SDZ NIM811, which block cytosolic calcium signaling and specifically the mitochondrial permeability transition pore (SDZ NIM811), also impaired **HBV** replication. Treatment of cells with compds. that increase cytosolic calcium levels by a variety of mechanisms rescued replication of an HBx-deficient **HBV** mutant. Transcription of viral RNA and production of viral capsids were only minimally affected by these treatments. These results define a functional signaling circuit for **HBV** replication that includes calcium signaling and activation of cytosolic signaling pathways involving Src kinases, and they suggest that these pathways are stimulated by HBx acting on the mitochondrial transition pore.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1995:388864 BIOSIS
DOCUMENT NUMBER: PREV199598403164
TITLE: Pharmacology and clinical use of foscarnet.
AUTHOR(S): Gerard, Laurence; Salmon-Ceron, Dominique [Reprint author]
CORPORATE SOURCE: Dep. Intern. Med., Cochin Hospital, 27 rue du fg Saint-Jacques, 75679 Paris Cedex 14, France
SOURCE: International Journal of Antimicrobial Agents, (1995) Vol. 5, No. 4, pp. 209-217.
ISSN: 0924-8579.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Sep 1995
Last Updated on STN: 13 Sep 1995

AB Foscarnet, licenced by Astra pharmaceutical products, is a pyrophosphate analogue that selectively inhibits replication of viruses in infected cells. It inhibits in vitro the replication of all herpes viruses, including human cytomegalovirus (HCMV) at concentrations of 100 to 300 mu-mol/l and has a dose-related inhibitory effect on HIV-1 virus, influenza virus and **hepatitis B virus**. It does not require intra-cellular phosphorylation for antiviral activity. Oral bioavailability of foscarnet is low (12-22%), and foscarnet must be administered intravenously. It is mainly eliminated unchanged by the kidneys. Mean half-life in plasma ranges from 3.4 to 5 h. For acute therapy, the currently recommended regimen is 60 mg/kg t.i.d. or 90-100 mg/kg b.i.d. In AIDS patients, foscarnet is an effective treatment of HCMV retinitis. Healing or stabilisation of lesions is obtained in 85-95% of patients after 2 weeks or 3 weeks therapy. For HCMV gastrointestinal disease, complete or partial response rates of 57-95% have been reported with foscarnet. The optimal maintenance dosage of foscarnet necessary in CMV infections in AIDS patients remains to be clearly established. Data from small samples size studies have shown that foscarnet decreased significantly circulating levels of HIV antigen in AIDS patients with HCMV disease. Foscarnet is an effective treatment for acyclovir-resistant herpes simplex virus and for acyclovir-resistant varicella-zoster virus (40 mg/kg every 8 h). In patients with immunosuppression not HIV-related HCMV infections, particularly interstitial pneumonia in transplant recipients, experience with foscarnet is limited. The major adverse effect of foscarnet is reversible renal dysfunction, due to acute tubular toxicity. It may be partially prevented by hyperhydratation during the treatment. Fluctuations in serum **calcium** and phosphore levels, with both increase and decrease are also frequent adverse reactions. Most clinical symptoms are related to decrease in ionized **calcium** levels. Hyperphosphatemia, a clinically benign phenomenon, reflects the incorporation of foscarnet in bone. Penile ulcerations have been described and may result from mucocutaneous direct toxicity of foscarnet eliminated in urine. Although relapses frequently occur after a few months of maintenance therapy. foscarnet that shows a marked activity against HCMV in vitro, has allowed important progress in therapy of HCMV infections in AIDS patients

L4 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1991:522714 BIOSIS
DOCUMENT NUMBER: PREV199192134174; BA92:134174
TITLE: EFFECTIVENESS OF HISTOPATHOLOGICAL DIAGNOSES IN DYSFUNCTION OF HEPATIC TRANSPLANTATION REVIEW OF 146 HISTOPATHOLOGICAL STUDIES FROM 53 TRANSPLANTS.
AUTHOR(S): COLINA F [Reprint author]; MOLLEJO M; MORENO E; ALBERTI N; GARCIA I; GONEZ-SANZ R; CASTELLANO G
CORPORATE SOURCE: DEP ANATOMIA PATOL, HOSP "12 OCTUBRE," CTRA ANDAKYCUA KM 5400, 28041 MADRID, SPAIN
SOURCE: Archives of Pathology and Laboratory Medicine, (1991) Vol. 115, No. 10, pp. 998-1005.
CODEN: ARPAAQ. ISSN: 0363-0153.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 19 Nov 1991
Last Updated on STN: 20 Nov 1991

AB In 47 patients who underwent 53 liver transplantations and immunosuppression with cyclosporine (**cyclosporin** A), methylprednisolone sodium succinate and antithymocyte globulin, 146 histopathological studies were performed (138 biopsies, six hepatectomies, and two autopsies). The following microscopical diagnoses were made: 43 acute rejections (29.**4**%), six chronic rejections (**4**.1%), 18 liver blood perfusion changes (12.3%), 15 biliary changes (10.2%), 10 cases of functional cholestasis (6.8%), two drug reactions (1.3%), two **hepatitis B virus** recurrences (1.3%), 11 opportunistic viral infections (7.5%), 18 minimal changes (12.3%), two nonclassifiable changes (1.3%), and 19 plurietiological changes (13%). A histopathological diagnosis of acute rejection was made in 31 transplants (58.**4**%). In 22 (71%) of them, acute rejection was diagnosed with the protocol biopsy specimen that was obtained during the second posttransplant week. Leukocyte counts and serum bilirubin and enzyme levels were obtained on the same day that the hepatic biopsy specimens were taken. There was no significant statistical difference between the mean serum data that accompanied each histopathological diagnosis, allowing identification of a characteristic biochemical profile for the causes of graft dysfunction. We report a detailed description of the microscopical findings of each diagnosis and the following conclusions: (1) Acute rejection is the most frequent cause of hepatic dysfunction and has an early appearance during the posttransplant period. (2) Histopathological findings can identify the causes of the dysfunction. (3) There is no specific biochemical pattern to differentiate these causes. This may be due to the frequent combination of etiological factors in every dysfunction episode.

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#1	Search **cyclosporin A and hepatitis B**	14:04:13	106

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1: Hepatogastroenterology. 1988 Jun;35(3):121-4. Related Articles, Links

Effects of verapamil on estimated hepatic blood flow in patients with HBsAg-positive cirrhosis.

Lay CS, Tsai YT, Kong CW, Lee FY, Lee SD, Chen KY, Chiang BN, Lo KJ.

Department of Medicine, Veterans General Hospital, Taipei, Taiwan, R.O.C.

Acute and chronic effect of verapamil on estimated hepatic blood flow were investigated in 12 patients with HBsAg-positive cirrhosis and portal hypertension. Acute administration of verapamil results in a significant increase (8%) in estimated hepatic blood flow (p less than 0.05). However, after chronic continued administration of verapamil, the mean value of estimated hepatic blood flow remains unchanged vis-a-vis basal values. Acute and chronic use of verapamil significantly reduced the hepatic venous pressure gradient for about an average of 20% at 1 hr after drug administration (p less than 0.05) and 18% 2 weeks later (p less than 0.05). This drop was associated with a significant reduction in hepatic vascular resistance by 39% at 1 hr later and by 37% 2 weeks later. Furthermore, the drop in hepatic vascular resistance was independent of any verapamil-induced changes in systemic hemodynamics. Verapamil significantly increased the indocyanine green plasma clearance and extraction ratio after acute or chronic use of the drug. We conclude that in patients with HBsAg-positive cirrhosis, the mechanism of verapamil in reducing the hepatic venous pressure gradient is predominantly by inducing a drop in hepatic portal vascular resistance.

PMID: 3402902 [PubMed - indexed for MEDLINE]

1: J Immunol. 1991 May 1;146(9):3138-44. Related Articles, Links

Cyclosporin A modulates the course of woodchuck hepatitis virus infection and induces chronicity.

Cote PJ, Korba BE, Steinberg H, Ramirez-Mejia C, Baldwin B, Hornbuckle WE, Tennant BC, Gerin JL.

Division of Molecular Virology and Immunology, Georgetown University Medical Center, Rockville, MD 20852.

Immunosuppression is known to influence the state of chronic hepatitis B virus infection, and is thought to increase the risk of developing chronic infection in newly exposed individuals. Cyclosporin A (CsA), an immunosuppressive agent that inhibits Th cell function, was administered to woodchucks chronically infected with woodchuck hepatitis virus (WHV), and resulted in a decreased severity of chronic hepatitis and an increased viremia during the treatment. Adult woodchucks inoculated with WHV and given CsA for 14 wk had increased viremias, decreased acute phase liver injury, and developed chronic infections at a higher rate compared with immunocompetent woodchucks given virus alone (chronicity in seven of seven WHV + CsA + vs zero of nine WHV + CsA-; p less than 0.001). These results in a relevant animal model of hepatitis B virus infection indicate: 1) that liver injury in acute hepadnavirus infections is immune-mediated and not a direct cytopathic effect of virus replication; 2) that Th cells function in the inflammatory response and in the immunologic control of hepadnavirus infection; and 3) that suppression of Th cell function in acute hepadnavirus infection decreases liver injury but alters the outcome of infection in favor of chronicity. These results also suggest continued challenges in the application of CsA in liver transplantation for hepatitis B virus-induced diseases.

PMID: 1826706 [PubMed - indexed for MEDLINE]

1: Nephrol Dial Transplant. 1990;5(7):525-30. Related Articles, Links

Viral hepatitis in HBsAg-positive renal transplant patients treated with cyclosporin and steroids.

Sandrini S, Callea F, Cristinelli L, Savoldi S, Setti G, Scaini P, Scolari F, Scalzini A, Pizzoccolo G, Maiorca R.

Institute of Nephrology, University and Spedali Civili, Brescia, Italy.

This study reports clinical, serological and immunomorphological observations on viral hepatitis in 14 HBsAg-positive renal transplanted patients treated with cyclosporin and steroids. Eleven patients who were HBsAg positive before transplantation developed signs of hepatitis. This was due to HBV in six cases and progressed into a mild chronic disease. The remaining five subjects lacked signs of HBV reactivation. The hepatitis, attributed to non-A non-B agents, recovered completely. Two more patients became HBsAg positive after transplantation both developed acute hepatitis, respectively drug and HBV related. Transition into chronicity occurred only in the latter case. The results seem to indicate: (1) the possibility of a high incidence of non-B virus hepatitis in HBsAg-positive transplanted patients under cyclosporin treatment; (2) a good prognosis in non-B hepatitis as compared to hepatitis B for the same patient group; and (3) a mild degree of disease activity in cases who develop chronic hepatitis.

PMID: 2130300 [PubMed - indexed for MEDLINE]

1: Hepatology. 1995 Jul;22(1):36-43. Related Articles, Links

Effect of immunosuppressive and antiviral agents on hepatitis B virus replication in vitro.

McMillan JS, Shaw T, Angus PW, Locarnini SA.

Victorian Infectious Diseases Reference Laboratory, Fairfield Hospital, Australia.

Hepatitis B virus (HBV) DNA-transfected hepatoma cells were incubated with the immunosuppressive agents prednisolone, azathioprine, and cyclosporin A (CsA) and the antiviral agents ganciclovir and foscarnet to investigate the effects of these compounds on HBV replication. Prednisolone and azathioprine increased intracellular viral DNA and RNA levels approximately twofold and fourfold, respectively. Treatment with CsA did not alter the levels of viral RNA or DNA. A combination of all three immunosuppressive agents increased the level of intracellular viral DNA eightfold, indicating an additive effect. Incubation of the cells in the presence of foscarnet decreased levels of both single-stranded and relaxed circular viral DNA, and in the presence of ganciclovir decreased the levels of relaxed circular viral DNA, predictable effects from their known mechanism of action. The stimulatory effect on viral replication induced by the combination of immunosuppressive agents was substantially inhibited by ganciclovir-foscarnet treatment. These observations could have implications for the management of recurrent HBV infection after liver transplantation.

PMID: 7601429 [PubMed - indexed for MEDLINE]

1: Z Gastroenterol. 1988 May;26(5):265-70. Related Articles, Links

[Cyclosporin A in chronic active hepatitis. Results of a pilot study of 20 patients]

[Article in German]

Friedrich K, Henning H.

Klinik Fohrenkamp der Bundesversicherungsanstalt fur Angestellte, Molln/Lauenburg.

In 20 patients suffering from advanced chronic active hepatitis, type B or NANB, the therapeutic effect of cyclosporin A was studied. 15 of these patients already showed cirrhotic transformations and partial liver dysfunctions. In 15 cases an unsuccessful pretreatment with glucocorticoids and/or azathioprine had been performed. Only 3 patients showed an improvement of biochemical and morphological findings under treatment with cyclosporin. In spite of complete normalisation of the biochemical data in another case the morphologic aspects of a liver biopsy remained unchanged. Except for one case of obvious hepatoxicity no serious side effects of cyclosporin were observed under a therapeutic blood concentration between 200 and 400 ng/ml. From our observations we conclude that cyclosporin only in rare cases of advanced chronic active hepatitis may be promising. Furthermore we could not detect any particular criteria for predicting a response to cyclosporin in advance.

PMID: 3136600 [PubMed - indexed for MEDLINE]

1: Int J Immunopharmacol. 1981;3(3):301-5. Related Articles, Links

T cell subsets in patients with acute and chronic HBV infection, primary biliary cirrhosis and alcohol induced liver disease.

Thomas HC.

The proportions of inducer and cytotoxic/suppressor T cells and their concentration in peripheral blood have been determined in patients with acute and chronic type B hepatitis, hepatitis B virus (HBV) carriers with normal hepatic histology, patients with alcohol-induced liver disease (ALD), primary biliary cirrhosis (PBC) and chronic extrahepatic cholestasis. During acute type B hepatitis the inducer/suppressor ratio was decreased due to an increase in suppressor cell concentrations. When this ratio returned to normal the HBs antigen was cleared and HBs antibody was detectable. Similar abnormalities were found in patients with HBs + ve chronic hepatitis. In HBs antigen-positive patients with normal histology, normal T cell subsets were found. In some patients with primary biliary cirrhosis the ratio of inducer to suppressor cells was low due to a reduction in the concentration of inducer cells and in others high due to a reduction in suppressor cells. Administration of cyclosporin A to the latter group produced an increase in the concentration of suppressor cells and there was an improvement in liver biochemistry. In alcohol-induced hepatitis and cirrhosis the ratio of inducer/suppressor cells was normal. Whether these imbalances of the regulatory cells of the immune system in patients with chronic HBV-induced hepatitis and PBC are of primary or secondary importance is uncertain. The relationship of the depressed ratio to persistence of the hepatitis B virus is worthy of further study.

PMID: 6457007 [PubMed - indexed for MEDLINE]